

PCT

WORLD INTELLECTUAL
International Bureau

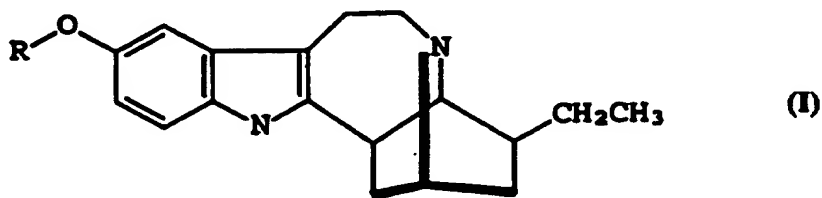
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/55, C07D 487/18		A1	(11) International Publication Number: WO 96/03127
			(43) International Publication Date: 8 February 1996 (08.02.96)
(21) International Application Number: PCT/US95/09136			(81) Designated States: CA, MX, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.
(22) International Filing Date: 25 July 1995 (25.07.95)			
(30) Priority Data: 280,187 25 July 1994 (25.07.94) US			
(71) Applicant: NDA INTERNATIONAL, INC. [US/US]; 46 Oxford Place, Staten Island, NY 10301 (US).			
(72) Inventors: MASH, Deborah, C.; University of Miami, Dept. of Neurology, 1501 Northwest 9th Avenue, Miami, FL 33136 (US). SANCHEZ-RAMOS, Juan; University of Miami, 1501 Northwest 9th Avenue, Miami, FL 33136 (US). HEARN, W., Lee; 1 Bob Hope Road, Miami, FL 33136-1133 (US).			
(74) Agents: BEAUMONT, William, E. et al.; Oblon, Spivak, McClelland, Maier & Neustadt, P.C., 4th floor, 1755 Jefferson Davis Highway, Crystal Square Five, Arlington, VA 22202 (US).			

(54) Title: A METHOD OF TREATING CHEMICAL DEPENDENCY IN MAMMALS AND A COMPOSITION THEREFOR

(57) Abstract

An essentially pure noribogaine compound having formula (I) wherein R is hydrogen or a hydrolyzable group of formula (II) wherein X is an unsubstituted C₁-C₁₂ group or a C₁-C₁₂ group substituted by lower alkyl or lower alkoxy groups, wherein the noribogaine compound having the hydrolyzable group hydrolyzes *in vivo* to form 12-hydroxy ibogamine.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Description

A Method Of Treating Chemical Dependency
In Mammals And A Composition Therefor

Technical Field

The present invention provides a method of treating chemical dependency in mammals and a composition therefor.

Background Art

Ibogaine is one of at least 12 alkaloids found in the Tabernanthe iboga shrub of West Africa. The indigenous peoples have used the drug in ritual, ordeal or initiation potions in large dosages and as a stimulant in smaller doses. One of the earliest European references to the drug was made by Professor Baillon on the Mar. 6th, 1889 session of the Linnaean Society in Paris during which he described samples obtained by Griffon de Bellay from Gabon and the French Congo.

Early isolation, and identification of ibogaine was accomplished by Dybowski and Landrin (Compt. rend. ac. sc. 133:748, 1901); Haller and Heckel (ibid. 133:850); Lambert and Heckel (ibid. 133:1236) and Landrin (Bull. sc. pharm. 11:1905).

There was little interest in the drug until Raymond-Hamet and his associates Rothlin, E. and Raymon-Hamet published the "Effect of Ibogaine on the Isolated Rabbit Uterus" in 1938 (Compt. rend. soc. biol. 127:592-4). Raymond-Hamet continued to study the drug for a period of 22 years, and singularly published 9 papers: Pharmacological Action of Ibogaine (Arch. intern. pharmacodynamie, 63:27-39, 1939), Two physiological Properties Common to Ibogaine And Cocaine (Compt. rend. soc. biol. 133:426-9, 1940), Ibogaine And Ephedrine (Ibid. 134:541-4, 1940), Difference Between Physiological Action of Ibogaine And That of Cocaine (Ibid. 211:285-8, 1940), Mediate And Intermediat Effects of Ibogain On The Intestine (Compt. rend. soc. biol. 135 176-79, 1941), Pharmacologic Antagonism

Of Ibogain (Compt. rend. 212:768-771, 1941), Some Color Reactions Of Ibogaine (Bull. soc. chim. Biol., 25:205-10, 1943), Sympathicosthenic Action of Ibogaine On The Vessels Of the Dog's Paw (Compt. rend 223:757-58, 1946), and Interpretation Of The Ultraviolet Absorption Curves Of Ibogaine And Tabernanthine (Ibid. 229:1359-61, 1949).

Vincent, conducted work on ibogaine in collaboration with Sero, Inhibiting Action Of Tabernanthe Iboga On Serum Cholinesterase (Compt. rend. Soc. Biol. 136:612-14, 1942). Vincent published five other papers: The Ultraviolet Absorption Spectrum Of Ibogaine (Brustier, B., Vincent D., & Sero, I., (Compt. rend., 216:909-11, 1943), Detection of Cholinesterase Inhibiting Alkaloids (Vincent, D. & Beaujard, P., Ann. pharm. franc. 3:22-26, 1945), The Cholinesterase Of The Pancreas: Its Behavior In the Presence Of Some Inhibitors In Comparison With The Cholinesterases of Serum And Brain (Vincent, D. & Lagreu, P., Bull. soc. chim. biol. 31:1043-45, 1949); and two papers, which he and Raymond-Hamet co-authored: Action of some Sympathicosthenic Alkaloids on the cholinesterases (Compt. rend. soc. biol., 150:1384-1386, 1956) and On Some Pharmacological Effects Of Three Alkaloids Of Tabernanthe Iboga, Bailion: Ibogaine, Iboluteine And Tabernanthine (Compt. rend. soc. biol., 154:2223-2227, 1960).

The structure of ibogaine was investigated by Dickel et al. (J.A.C.S. 80, 123, 1958). The first total synthesis was cited by Buchi et al. (J.A.C.S., 87, 2073, 1965) and (J.A.C.S. 88, 3099, 1966).

In 1956 Salmoiraghi and Page elucidated the relation between ibogaine and serotonin (J. Pharm & expt. ther. 120 (1), 20-25, 1957.9). Contemporaneously, Schneider published three papers. The first, Potentiation Action Of Ibogaine on Morphine Analgesia was done in collaboration with Marie McArthur (Experiential 12:323-324, 1956), while the second was Neuropharmacological Studies of Ibogaine: An Indole Alkaloid

-3-

With Central-Stimulant Properties (Schneider, J.A. & Sigg, E.B., Annals of N.Y. Acad. of Sciences, Vol. 66:765-776, 1957). The third was An Analysis of the Cardiovascular Action Of Ibogaine HCL (Schneider, J.A. & Rinehard, R.K., Arch. int. pharmacodyn., 110:92-102, 1957).

The stimulant properties of ibogaine were further investigated by Chen and Bohner, (J. Pharm. & Expt. Ther., 123 (3): 212-215, 1958). Gerson and Lang published A Psychological Study Of Some Indole Alkaloids (Arch. intern. pharmacodynamie, 135:31-56, 1962).

In 1963, Bunag evaluated certain aspects of the relationship between ibogaine and Substance P (Bunag, R.D.; Walaszek, E.J. The Cardiovascular Effects of Substance P in the Chicken Ann. N.Y. Acad. Sci. 104, Part 1, 437-48, 1963).

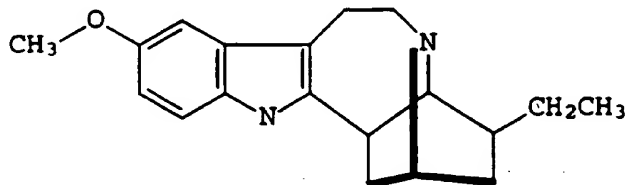
In 1969, Naranjo reported on the effects of both ibogaine and harmine on human subjects in his paper: Psychotherapeutic Possibilities Of New Fantasy-Enhancing Drug (Clinical Toxicology, 2 (2): 209-224, June 1969).

As a doctoral thesis in 1971, Dhahir published A Comparative Study of The Toxicity Of Ibogaine And Serotonin (University Microfilm International 71-25-341, Ann Arbor, Mich.). This thesis provides an overview of much of the work accomplished with ibogaine.

Additionally, studies of interest also include: The Effects Of Some Hallucinogens On Aggressiveness of Mice And Rats (Kostowski et al., Pharmacology 7:259-263, 1972), Cerebral Pharmacokinetics Of Tremor-Producing Harmala And Iboga Alkaloids (Zetler et al., Pharmacology 7 (40): 237-248, 1972), High Affinity 3H-Serotonin Binding To Caudate: Inhibition By Hallucinogenic And Serotonergic Drugs (Whitaker, P. & Seeman, P., Psychopharmacology 59:1-5, 1978, Biochemistry), Selective Labeling Of serotonin Receptors by d-(3H) Lys rgic Acid Diethylamide In Calf Caudate (Proc. natl. acad. sci., USA, Vol. 75, No. 12, 5783-5787, Dec. 1978,

Biochemistry) and A Common Mechanism Of Lysergic Acid, Indolealkylamine And Phenthyllamine Hallucinogens: Serotonergic mediation of Behavioral Effects In Rats (Sloviter, Robert et al., J. Pharm. Expt. Ther., 214 (2):231-238, 1980).

Ibogaine is an alkaloid of the formula:



Ibogaine

It is an intriguing structure, which combines the structural features of tryptamine, tetrahydrohavaine and indoloazepines. The total synthesis of ibogaine has been reported. See Buchi, G. et al, J. Am. Chem. Soc., 1966, 88, 3099 (1966); Rosenmund, P. et al, Chem. Ber., 108, 1871 (1975) and Huffman et al, J. Org. Chem., 50, 1460 (1985).

More recently, it was discovered that ibogaine was effective as an "interrupter" of withdrawal and dependence for a variety of agents, such as heroin, cocaine, alcohol, amphetamine, caffeine and nicotine, for example. See U.S. Patent Nos. 4,587,243, 4,857,523, 4,499,096, 5,026,697 and 5,152,994. Despite a certain and potent effect, however, studies have failed to elucidate a mechanism of action. For example, studies of the binding properties of ibogaine to a large number of neurotransmitter receptor clones has failed to detect any significant pharmacology activities that would explain its mechanism of action.

Nevertheless, administration of ibogaine has proven to be generally effective in mammals for treating chemical dependence. Such dependencies include those to substances

which are as diverse as heroin, cocaine, alcohol and nicotine.

However, the effects of ibogaine are relatively short in duration and are generally not observed beyond 24 hours after administration. Thus, a need exists for an agent which is as effective as ibogaine in treating chemical dependencies, yet which is longer lasting in effect.

Disclosure of the Invention

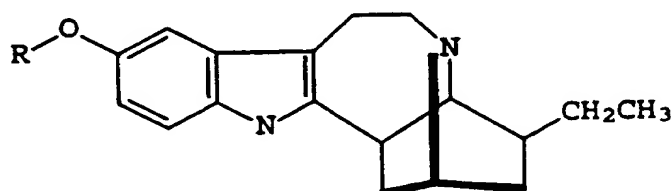
Accordingly, it is an object of the present invention to provide an agent which, when administered to mammals, can reduce craving for addictive substances therein. ✓

It is, moreover, an object of the present invention to provide an agent for treating chemical dependency in mammals which is longer acting than ibogaine on the mammalian host.

It is also an object of the present invention to provide a pharmaceutical composition for reducing craving for addictive substances in mammals.

Further, it is also an object of the present invention to provide a method of treating chemical dependency in a mammal, which entails administering to a mammal in need thereof an amount of essentially noribogaine or a hydrolyzable derivative thereof.

These advantages and others are provided by an essentially pure noribogaine compound having the formula:



-6-

wherein R is hydrogen or a hydrolyzable group of the formula:



wherein X is an unsubstituted C₁-C₁₂ group or a C₁-C₁₂ group substituted by lower alkyl or lower alkoxy groups, wherein the noribogaine having the hydrolyzable group hydrolyzes *in vivo* to form 12-hydroxy ibogamine.

Brief Description of the Drawings

Figure 1 is a graphical plot of ibogaine pharmacokinetics in a human as a function of blood concentration versus time.

Figure 2 is a graphical plot of noribogaine (12-hydroxy ibogamine) pharmacokinetics in a human as a function of blood concentration versus time.

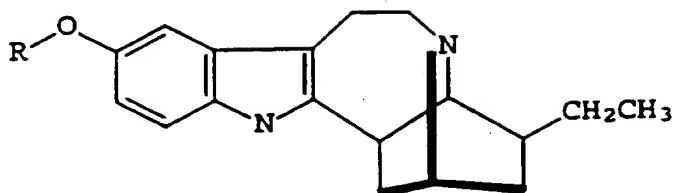
Best Mode for Carrying Out the Invention

The present invention is predicated upon the surprising discovery of a new class of noribogaine compounds which have a greater and longer lasting activity in mammals than ibogaine for reducing craving for addictive substances, and treating chemical dependency.

In accordance with the present invention, it has been surprisingly discovered that noribogaine, a metabolite of ibogaine, and certain hydrolyzable esters of noribogaine have a much longer lasting effect than ibogaine. Thus, by administering the compounds of the present invention and compositions containing the same, a prolonged anti-craving effect may be obtained in mammals.

Generally, the present invention provides compounds of the formula:

-7-



wherein R is hydrogen or a hydrolyzable group, such as hydrolyzable esters of from about 1 to 12 carbons. Such compounds may be administered either as single compounds, mixtures of compounds or as composition for reducing craving in mammals and/or treating chemical dependency.

Generally, in the above formula, R is hydrogen or a group of the formula:



wherein X is a C₁-C₁₂, group, which is unsubstituted or substituted. For example, X may be a linear alkyl group such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl or n-dodecyl, or a branched alkyl group, such as i-propyl or sec-butyl. Also, X may be a phenyl group or benzyl group, either of which may be substituted with lower alkyl groups or lower alkoxy groups. Generally, the lower alkyl and/or alkoxy groups have from 1 to about 6 carbons. For example, the group R may be acetyl, propionyl or benzoyl. However, these groups are only exemplary.

Generally, for all groups X, they may either be unsubstituted or substituted with lower alkyl or lower alkoxy groups. For example, substituted X may be o-, m- or p-methyl or methoxy benzyl groups.

The compounds of the present invention specifically include all those of the formula (I) which includes 12-

hydroxy-ibogamine or those compounds which are hydrolyzed *in vivo* in mammals to form 12-hydroxy ibogamine.

These compounds may be used singly or in admixture with one or more of such compounds.

Furthermore, the compounds of the present invention may be used either in the free base form or in the form of a pharmaceutically acceptable acid addition salt, such as, for example, the hydrochloride, hydrobromide, sulfate or phosphate salt.

The compounds of the present invention may be made in several ways. For example, 12-hydroxy ibogamine (noribogaine) may be synthesized by O-demethylation of ibogaine. This may be effected, for example, by reacting ibogaine with boron tribromide/methylene chloride at room temperature and isolating and purifying the product using known methodologies.

From noribogaine, any of the hydrolyzable esters of the present invention may be synthesized by reacting noribogaine with an appropriate anhydride or acyl chloride with or without a catalyst, such as pyridine. For example, 12-hydroxy ibogamine can be reacted with acetic anhydride in the presence of pyridine catalyst to yield 12-acetoxyibogamine. This specific example may be modified by using the appropriate anhydride or acyl chloride to form any of the present esters. The anhydrides and/or acyl chlorides so used are all either known compounds or can be synthesized from known compounds using known reactions.

See also J. Org. Chem., vol. 59,8 (1994), Repke et al.

In accordance with the present invention, any single compound or mixture of compounds may be administered to a mammal in the amounts described in any one of U.S. Patent Nos. 4,587,243; 4,857,523, 4,499,076 5,026,697 or 5,152,994, each of which is incorporated herein in the entirety. Moreover, administration thereof may be from one to three times daily depending upon the need of the patient mammal to

reduce craving for the substance of interest.

Generally, the present compounds or mixtures thereof are administered in an amount of from about 0.01 mg to about 100 mg per kg of body weight per day. The precise amount administered will vary as needed.

The present invention also provides pharmaceutical compositions for treating drug dependency in mammals. These compositions generally contain one or more of the compounds of the present invention in combination with a pharmaceutically acceptable carrier. Other excipients may also be added.

In accordance with the present invention, the compounds or compositions thereof may be administered in any manner, such as orally, intravenously, intramuscularly or interperitoneally. The present compositions may be compounded in any conventional manner using conventional excipients. For example, the present compositions may be compounded as capsules, tablets, pills, powders or solutions. Additionally, excipients, such as conventional binders and/or fillers, may be used.

Furthermore, the excipient and carrier formulations used for the present compositions may be those as described, for example, in U.S. Patent Nos. 5,192,746 and 5,132,408. However, any conventional and pharmaceutically acceptable excipient may be used.

Generally, any means of formulating the present compounds or compositions may be used. For example, any suitable solid or liquid formulation may be used. Moreover, any conventional time-release formulation may be used with the compounds and solid compositions of the present invention.

Furthermore, the present compounds or compositions containing the same may be administered in any manner, such as, for example, orally, by suppository or by rectal infusion in the same manner as described in any of U.S. Patent Nos. 4,587,243, 4,857,523, 4,499,096, 5,026,697 and 5,152,994.

In accordance with the present invention, the present invention may be used to treat chemical dependency in mammals for any substance which has the tendency to lead to such dependency. Such substances may be, but are not limited to, heroin, cocaine, PCP, marijuana, alcohol, nicotine, methamphetamine, opium, methadone, hycodan, morphine and caffeine. Generally, the present compounds are administered in an amount of about 0.01 mg to about 100 mg per kg of body weight per day. The compounds may be administered from one to up to several times per day, if necessary.

Of course, the chemical dependency treated in accordance with the present invention is not limited to heroin, cocaine, PCP, marijuana, alcohol, nicotine and caffeine. Rather, any type of chemical dependency may be treated thereby. As used herein, the term "chemical dependency" is intended to mean dependency of a mammal upon any single chemical, mixtures of chemicals, natural or synthetic product or mixture of all of the above which tend to promote repeated self-administration thereof. The mammals treated herein may be humans, cats, dogs, livestock or laboratory animals, such as rats, mice or rabbits, for example.

Furthermore, although the present invention is generally used in conjunction with humans, any mammals, such as dogs, cats, livestock or poultry may be treated as needed with adjustments being made for differences in body weight.

Quite surprisingly, in accordance with the present invention, it has been discovered that the present compounds, when administered, have a much longer lasting effect in reducing chemically dependent cravings in the mammalian body than ibogaine.

Furthermore, in accordance with the present invention, the long plasma half-life of the present compounds has been correlated with the long duration of psychoactive effects in mammals. Generally, the plasma half-life of the present

-11-

compounds in mammals is from about 2 to 8 hours. However, the present compounds have been detected in human plasma and urine samples at four weeks post administration.

Finally, it is noted that for the sake of convenience, the compounds of the present invention may also be referred to as "noribogaine" or derivatives thereof.

In order to more fully describe the present invention, reference will now be made to certain examples which are provided solely for illustration and are not intended to be limitative.

EXAMPLE

An amount of ibogaine was administered to a human patient, and the plasma concentration of both ibogaine and a metabolite thereof, 12-hydroxy ibogamine, were observed as a function of time.

Figure 1 illustrates the result of administering a certain dosage of ibogaine to a human patient, where the plasma concentration of ibogaine is measured over time. In essence, a peak plasma concentration of about 1,100 ng/ml is observed at administration. It is also notable that at about 11 hours after ibogaine administration, plasma concentration of ibogaine diminished to less than 400 ng/ml. After about 24 hours, plasma concentration diminished to less than 200 ng/ml. Thus, ibogaine is rather quickly eliminated by the patient.

By contrast, Figure 2 illustrates the variation of noribogaine plasma concentration with time as a metabolite from the same ibogaine administration described above. In essence, a peak plasma concentration of noribogaine of about 590 ng/ml was reached only after about 11 hours from administration. Thereafter, even at 24 hours, a plasma concentration of greater than 500 ng/ml was observed. Thus, noribogaine exhibits a much longer plasma half-life than

-12-

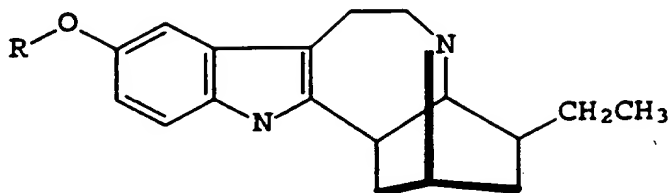
ibogaine and, thus, is much longer lasting in effect.

The present invention may also be advantageously used with laboratory animals in assessing the addictive potential in humans of present and prospective future addictive agents. As such, conventional methods of testing may be used in conjunction with the compounds and compositions of the present invention.

Clearly, numerous modifications and variations of the present invention are possible in light of the above teachings. It is, therefore, to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

Claims

1. An essentially pure noribogaine compound having the formula:



wherein R is hydrogen or a hydrolyzable group of the formula:



wherein X is an unsubstituted C₁-C₁₂ group or a C₁-C₁₂ group substituted by lower alkyl or lower alkoxy groups, wherein said noribogaine compound having said hydrolyzable group hydrolyses *in vivo* to form 12-hydroxy ibogamine.

2. The noribogaine compound of Claim 1, wherein X is C₁-C₆ group.

3. The noribogaine compound of Claim 2, wherein X is methyl or ethyl.

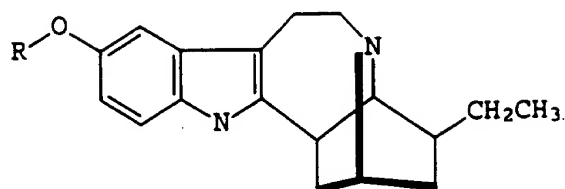
4. The noribogaine compound of Claim 1, wherein R is benzoyl.

5. The noribogaine compound of Claim 1, wherein R is hydrogen.

6. A pharmaceutical composition for treating chemical dependency in a mammal, which comprises:

-14-

a) an amount of one or more noribogaine compounds having the formula:



wherein R is hydrogen or a hydrolyzable group of the formula:



wherein X is an unsubstituted C_1-C_{12} group or a C_1-C_{12} group substituted by lower alkyl or lower alkoxy groups, effective to reduce craving for a chemical substance in said mammal, thereby treating the chemical dependency, and

b) a pharmaceutically acceptable excipient.

7. The pharmaceutical composition of Claim 6, wherein in said noribogaine compound, X is C_1-C_6 group.

8. The pharmaceutical composition of claim 7, wherein X is methyl or ethyl.

9. The pharmaceutical composition of Claim 6, wherein R is benzoyl.

10. The pharmaceutical composition of Claim 6, wherein said R is hydrogen.

11. A method of treating chemical dependency in a mammal, which comprises administering to said mammal an amount

*See also
antiquated
claims to
pharmaceutical
composition*

-15-

of the noribogaine compound of Claim 1 or the pharmaceutical composition of Claim 6 effective to treat said chemical d pendency.

*Method of
treating
chemical dependency*

12. The method of Claim 11, wherein said mammal is human.

13. The method of Claim 11, wherein said chemical d pendency is to a substance selected from the group consisting of heroin, cocaine, alcohol, nicotine, amphetamine, methamphetamine, opium, methadone, hycodan, morphine and caffeine.

14. The method of Claim 11, wherein said noribogaine compound is 12-hydroxy ibogamine.

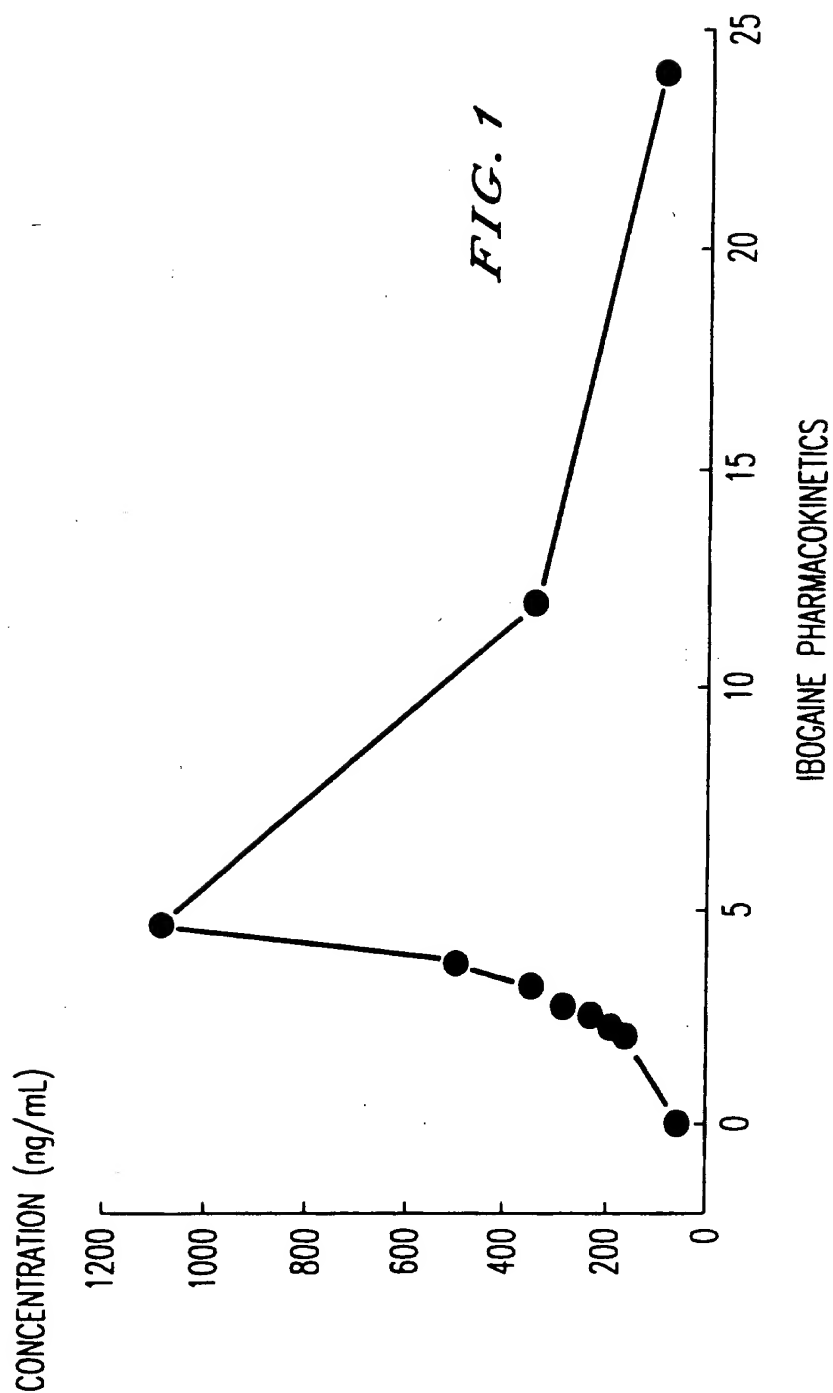
15. A method of treating addiction to a drug in a mammal in need thereof, which comprises administering to said mammal an amount of the noribogaine compound of Claim 1 or the pharmaceutical composition of Claim 6 effective to reduce craving or withdrawal symptoms or both for said drug.

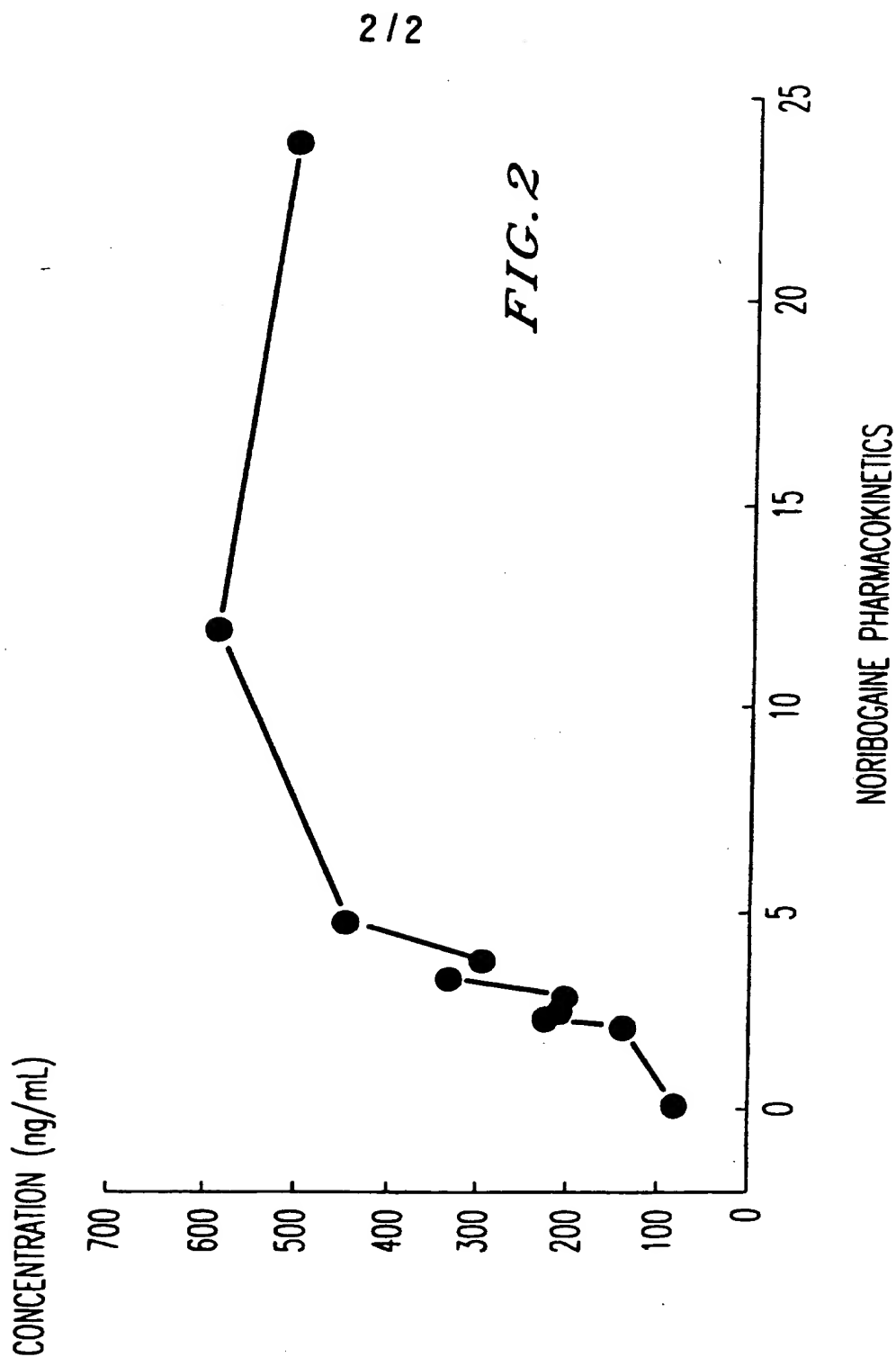
16. The method of Claim 15, wherein said mammal is human.

17. The method of Claim 15, wherein said drug is selected from the group consisting of heroin, cocaine, m thamphetamine, opium, methadone, hycodan, morphine, amphetamine, alcohol, caffeine and nicotine.

18. The method of Claim 15, wherein withdrawal symptoms from the drug are reduced.

1/2





INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/09136

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/55; C07D 487/18

US CL :514/214; 540/579

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/214; 540/579

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 3,516,989 (SALLAY ET AL) 23 June 1970, see column 1, lines 46-56 and column 6, lines 25-36 and 67-71.	1, 5, 6, 10
-----		-----
Y		1-4, 6-9, & 11-18
Y	H. BUNDGAARD, "DESIGN OF PRODRUGS" published 1985 by Elsevier (Amsterdam), pages 1-10, see pages 3-4.	1-4, 6-9, & 11-18
Y	T. HIGUCHI et al, "PRO-DRUGS AS NOVEL DRUG DELIVERY SYSTEMS" published 1975 by American Chemical Society (Washington), pages 1-50, see pages 47-48.	1-4, 6-9, & 11-18
Y	US, A, 5,152,994 (LOTSOF) 06 October 1992, see abstract.	11-18

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A* document defining the general state of the art which is not considered to be of particular relevance	* X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* E* earlier document published on or after the international filing date	* Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* A*	document member of the same patent family
* O* document referring to an oral disclosure, use, exhibition or other means		
* P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

15 SEPTEMBER 1995

Date of mailing of the international search report

12 OCT 1995

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer
KING L. WONG

Telephone No. (703) 305-1235